FDA Regulation of Controlled Substances: A Review of 2013, What to Expect in 2014

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Disclosure Statement

I have no financial relationships with proprietary entities that produce health care goods and services

The opinions and information in this presentation are my own and do not necessarily reflect the views and policies of the FDA

FDA Activities

- Guidance
  - Abuse Deterrent Formulations of Opioids
- Regulatory Actions
  - OxyContin and Opana ER
  - ER-LA opioid relabeling and PMRs
  - Zohydro approval
- Hydrocodone Combination Product Rescheduling

Guidance

DRAFT GUIDANCE ON ABUSE-DETERRENT FORMULATION (ADF) DEVELOPMENT

Draft ADF Guidance

- Earlier Guidance: Assessment of Abuse Potential of Drugs, issued January 2010
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf
- Discusses use of safety information from all areas of the NDA, including brief discussion of abuse-deterrent formulations

Abuse-Deterrent Opioids Guidance

- Opioids specially formulated to reduce abuse are one potentially important step toward creating safer opioids
- Guidance on their development was promised as part of ONDCP Rx Drug Abuse Plan (2011)
- Guidance on their development mandated under FDASIA*
  - Goal date January 9, 2013

* Food and Drug Administration Safety and Innovation Act

Abuse-Deterrent Opioids Draft Guidance: Purpose

- Reflect the state of the science of abuse deterrence (relatively new), and the need to take flexible while still taking a rigorous, science-based approach in evaluation and labeling of drugs as data accumulates

Abuse-Deterrent Opioids Draft Guidance: Highlights

- Goals: Two over-arching goals:
  - Encourage the development of successful abuse-deterrent formulations of opioids
  - Assure appropriate development and availability of generic drugs, reflecting their importance in US healthcare

- Accomplishing this: encouraging the use of successful abuse-deterrent formulations through accurate labeling

Highlights of Guidance

- Lays out development roadmap:
  - Scientific Studies relevant to assessing impact of formulation on abuse
  - Assessments FDA will use when looking at study data
  - Impact of data on labeling, including claim for abuse-deterrence
- Identifies areas additional scientific needs

Labeling Claims for ADFs

- Grouped according to source and type of data
  - Tier 1: Physical/Chemical Barriers to Abuse
    - Examples: data on crushing and extraction
  - Tier 2: PK Data
    - Clinical serum concentrations (e.g., Tmax, Cmax)
  - Tier 3: Demonstration of Reduced Abuse Potential
    - Clinical Abuse Potential Studies
  - Tier 4: Demonstration of Reduced Abuse
    - Postmarketing data on use and misuse of marketed product
- Differs according to technology used to create formulation

Needed Additional Scientific Work

- Characterizing the quantitative link between:
  - Changes in the pharmacokinetics of opioids in different formulations
  - Results of clinical studies using those same formulations
  - Differences in abuse in the community
- Characterizing the best methods to analyze clinical data on abuse
- Characterizing the best methods to analyze the impact of formulations on rates of abuse in the community

Issues

- Does not address how FDA will approach generics evaluation, approval, and withdrawal
- Does not set ‘bright line’ standard of what constitutes meaningful ‘abuse deterrence’
  - Will need more experience before we can set such a standard
    - To date, two decisions have been made with respect to specific formulations based on the totality of the data available to FDA
  - Need more data on the link between non-clinical and pre-market studies and post-market impact on abuse, overdose, and death

Regulatory Actions

1. OXYCONTIN AND OPANA ER

2. EXTENDED-RELEASE AND LONG-ACTING OPIOIDS RELABELING AND POST-MARKETING REQUIREMENT

3. ZOHYDRO

Actions on Oxycontin & Opana ER

- April 16, 2013: Oxycontin granted labeling as abuse-deterrent
  - The new labeling indicates that the product has physical and chemical properties that are expected to make abuse via injection difficult and to reduce abuse via the intranasal route (snorting)
- May 10, 2013: Opana ER determined not to have demonstrated abuse-deterrent properties
- Decisions based on scientific data from each application separately, drawing on principles from draft Guidance

Extended-Release and Long-Acting (ER-LA) Opioid Re-labeling and Post-marketing Study Requirement

Background

- Need for prescribers to understand risks of extended release long-acting (ER-LA) opioids
- Need to clearly describe the patient who could benefit from these drugs

- Considerable public comment on how best to label ER-LA opioids
  - Citizen's Petitions to change indications
  - Comments from Part 15 hearing held in 2012 on issue
- FDA concluded labeling revisions needed

Labeling Language

Old Language

- Xxx is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time

New Language

- Xxx is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

Additional Label Changes

- Urges prescribers to “assess each patient’s risk” for abuse before prescribing and to “monitor all patients regularly for the development of abuse”
- Boxed Warning: increased emphasis on risks, including abuse, overdose, death, and Neonatal Opioid Withdrawal Syndrome

Goals of Labeling Changes

- Move away from an indication based on a subjective severity scale
- Move towards individual assessment of the impact of the patient's pain, to determine both whether or not it is severe enough to warrant ER-LA opioids and whether alternatives would be inadequate
- Highlight potential risks of ER-LA opioids

Next Steps

- Companies have to submit responses to letters with labeling changes
- FDA working to change Medication Guide, Blueprint, Patient Medication Information to reflect new language

Post-Marketing Requirements

- FDA also concluded additional data were needed
- Studies and trials to be conducted by manufacturers of the ER-LA opioids to better assess:
  - the known risks of abuse, abuse, hyperalgesia, overdose and death when ER-LA opioids are used long-term
  - the relationship between opioid dose and duration and these risks
- Part of overall risk-benefit profile for ER-LA opioids

Approval of Single-Entity Hydrocodone Product (Zohydro)

Zohydro Approval

- Zohydro
  - Member of ER-LA opioids
    - Similar doses and anticipated uses as several other ER-LA opioids (e.g., oxymorphone, oxycodone, hydromorphone)
    - Meets statutory requirements for approval
- Reflects newly revised ER-LA opioid labeling
  - Responsive to Advisory Committee concerns about class
  - Increased safety information
  - New indication
  - Sponsor is required to participate in PMR studies
- Part of larger FDA efforts to improve the use of opioids
  - Augmented choice for patients
  - Allows users of high doses of hydrocodone to avoid use of acetaminophen and liver toxicity
  - Sponsor is working to develop ADF formulation

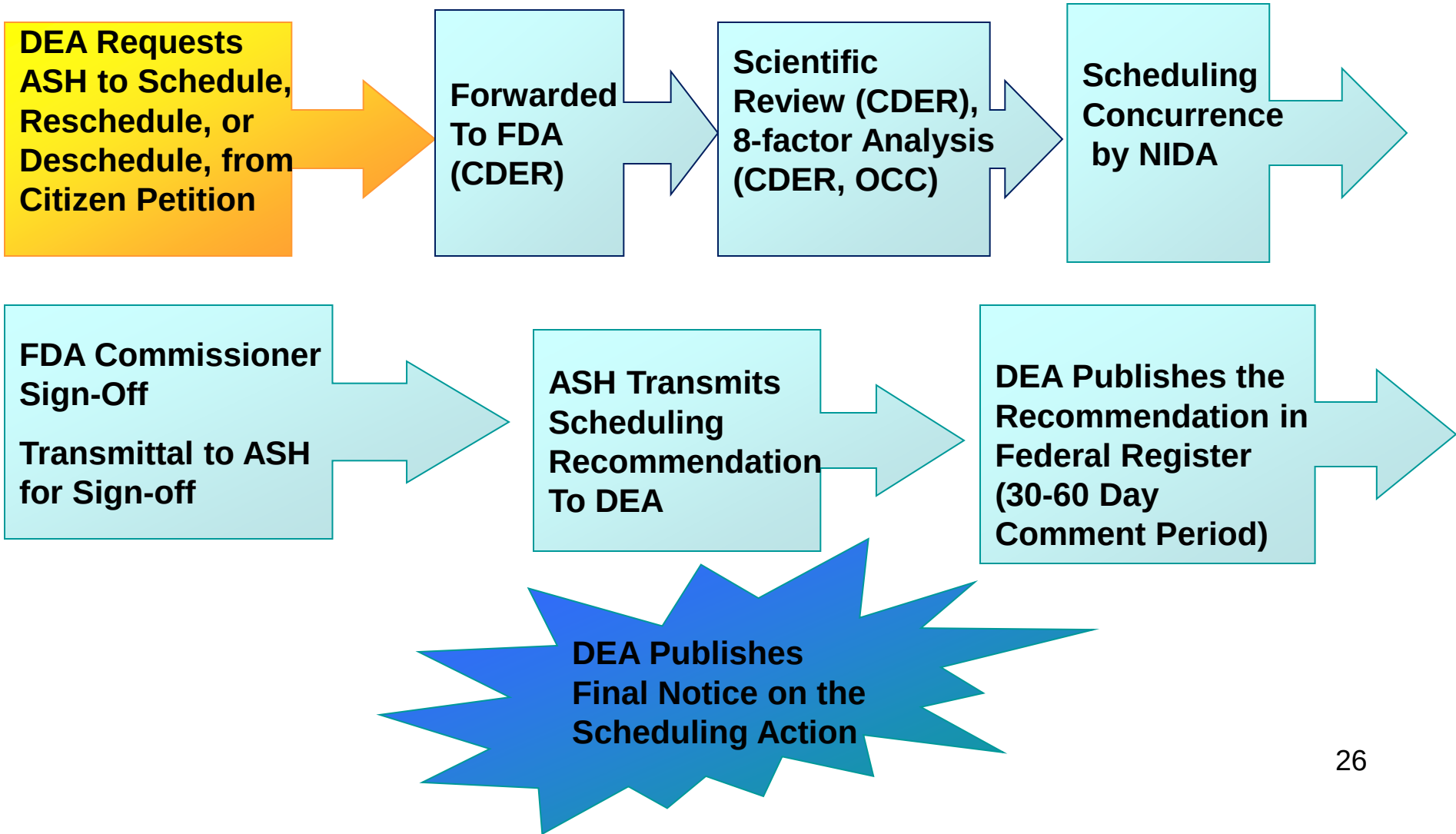
Scientific Assessments

HYDROCODONE COMBINATION PRODUCT (HCP)
RESCHEDULING

Background

- Hydrocodone is marketed only as combination products (HCPs) for pain and for cough-suppression
  - Ongoing abuse and misuse
  - Over 8 billion tablets dispensed last year!
- What is the appropriate level of control (‘Schedule’)for these products?
- Scheduling: FDA conducts scientific analysis and makes recommendation (through OASH) to DEA

Interagency Response to Drug Scheduling Petitions



Background: Impacts of Schedule II vs. III *

- Refills
  - No CII refills, but 90 days of drug can be prescribed by physician at a visit (3 scripts with a total of 90 day supply)
  - CIII: 180 days of drug can be prescribed by physician at a visit (1 Rx plus 5 refills)
    - Phone call-in renewals possible
- Prescribing
  - CII registration with DEA separate from CIII-V
  - State Laws may limit CII prescribing to physicians
- Security
  - CII custodial requirements higher than CIII for pharmacists, wholesalers, manufacturers and distributors

*Federal Law; some State laws differ

FDASIA Section 1139 on HCPs

- Calls for the Secretary of Health and Human Services to hold a public meeting on hydrocodone combo product upscheduling
- Requires FDA to solicit input from stakeholders including patients, healthcare providers and others “regarding the health benefits and risks, including the potential for abuse and the impact of up-scheduling of these products.”

FDA Work to Date

- FDA Scientific Analysis
  - Focused on 8 factors from CSA
  - Data sources: DAWN-ED, TEDS, FAERS, IMS, NPDS
- Public comment on public health impact:
  - Hydrocodone Upscheduling Advisory Committee January 24-25, 2013
    - Voted 19-10 to recommend upscheduling
  - Extensive Public Comment
    - Hydrocodone Docket: 768 comments

HCP Scheduling Process

- December 11, 2013 FDA sent to HHS the recommendation to reschedule hydrocodone combination products from C-III to C-II. This recommendation was concurred with separately by NIDA
- December 17th, 2013 HHS (through the OASH, Dr. Howard Koh) sent DEA the recommendation to reschedule hydrocodone combination products from C-III to C-II
- DEA analysis ongoing

Extensive FDA Activities

- FDA has a critical regulatory role:
  - Education of prescribers through Risk Evaluation and Mitigation Strategy (REMS)
  - **Review of products for abuse-deterrent effects (Oxycontin, Opana ER)**
  - **Development of abuse-deterrent formulations of opioids**
  - Work on drug packaging and labeling to reduce abuse and misuse
  - Development of new formulations of naloxone
  - **ER-LA opioid relabeling and PMRs**
  - **Single-entity hydrocodone (Zohydro) approval**
  - **Hydrocodone combination product upscheduling**
  - Support work to develop new non-abusable pain drugs
  - Scientific assessment of drugs for scheduling

Extensive FDA Activities (cont)

- Additional FDA role supporting important non-regulatory activities through collaboration and resources:
  - Development of model Patient Provider Agreement
  - Work on use of aggregate PDMP data
  - Work to support appropriate disposal of drugs

Summary

- Many other FDA activities not discussed
- We take our role seriously, have significantly expanded our activities to address opioids
  - Improved use of opioids
  - Appropriate access to pain treatment
- Within this broadened range of activities, our regulatory mission remains at the heart of FDA role in opioids
  - FDA will act within its authorities, based on science, in support of our public health mission